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International Journal of Obesity (1998) 22, Suppl 2, S15–S21

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Fit, fat and fat free: The metabolic aspects of weight control

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This paper examines the role of energy expenditure, especially physical activity related energy expenditure, in the metabolic aspects of body weight regulation. New data have emerged from studies conducted over the last decade, demonstrating that physical activity is a critical factor contributing to successful body weight regulation in lean and obese individuals. A growing number of prospective studies show the protective role of increased physical activity against weight gain over time. Also, individuals who are successful in long-term maintenance of a weight reduction are highly likely to also be physically active. Participation in physical activity is among the best predictors of success in weight maintenance. Physical activity facilitates weight maintenance through direct energy expenditure and improved physical fitness. The latter facilitates the amount and intensity of daily activities. Both components are of importance in relation to energy and substrate balance. Exercise may act as a substitute for an enlarged fat mass, in bringing about rates of fat oxidation commensurate with fat intake. Metabolic effects on lipid mobilization and oxidation and morphological/biochemical changes in the muscle fiber, contribute to this successful regulation of body weight. A limited number of studies indicate that, the minimal level of additional energy expenditure by physical exercise required for protection against gain in excessive body fatness, is around 12 kcal/kg body weight/d. In conclusion, the amount of energy expended in physical activity, mediated by several metabolic factors, may play an important role in body weight regulation.

Keywords: physical activity; body weight regulation; fat oxidation; muscle metabolism; weight maintenance; obesity; substrate balance; energy expenditure; body composition; fitness; exercise

Introduction

Controlling body weight is a problem faced by many people in today's society. Statistics published in most developed countries show that the prevalence of obesity is increasing at an alarming rate.[1] The serious health consequences may only become fully apparent in the distant future.

Studies in animals, and increasingly in controlled studies in humans, demonstrate the body has a complex and highly sophisticated system to regulate body weight and, in particular, to regulate fat stores. It has become clear that physical activity plays a vital role in this system. Perhaps the most convincing argument for this regulatory role is the observation that, with the exception of sumo wrestlers (who need high body mass for physical combat), the prevalence of obesity is almost zero for athletes. Also, those who leave sports, frequently experience an increase in body weight and fatness.

Much more difficult to prove, is the role of an inactive life-style in the etiology of obesity. Furthermore, there is a widespread view among the public, that exercise is ineffective in the control of body weight. This arises through the belief that the amount of exercise required to make a difference in weight is too great to be practical, or that the increase in energy raises appetite and food intake, negating the effect of the additional exercise. One of the major problems in analyzing the role of physical activity in body weight control, is the lack of valid information on long-term levels of daily physical activity in populations. To date, we can only make the case for the negative aspects of decreased activity levels on body weight regulation, by indirectly linking the prevalence of obesity with indicators of a sedentary lifestyle, such as cars per household or hours watching television per week.[2]

In this paper, the metabolic consequences of a sedentary lifestyle *vs* being physically active, will be discussed, and arguments and questions regarding its role in the regulation of body weight will be addressed.

Exercise, energy expenditure and physical fitness

It is important to realize that energy expenditure is related to both body size and body composition. It has frequently been hypothesized that energy imbalance

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has its origins in either a physiological or behavioral defect, leading to low levels of energy expenditure. Measurement of basal metabolic rate and standardized 24 h energy expenditure in a whole body calorimeter, refute this hypothesis by demonstrating that both are substantially higher in obese than in lean people.[3] Total daily energy expenditure (24 h EE) can be divided into several components: resting metabolic rate (RMR), which accounts for approximately 60–70% of 24 h EE; the energy costs of feeding (TEF), approximately 10% of 24 h EE; and the activity energy expenditure (AEE), which is the most variable component and may vary from 10–15% of 24 h EE in sedentary people, 30–40% in active people, to even 400% in endurance athletes under extreme circumstances.[4]

Since the average adult RMR is fairly close to 3.5 ml/kg/min oxygen or 1 kcal/kg body weight/h, the energy cost of activities can be expressed as multiples of resting metabolic rate or METs. The use of METs is a simple approach to quantify the level of exercise, taking body weight into account. An extensive and informative compendium of MET values for activities, was published by Ainsworth *et al.*[5] MET values provide an indication of intensity of physical activity and when summed over time, these values can be used to compare levels of physical activity between individuals or groups. MET measures also fit well with the concept of the physical activity ratio (PAR) or physical activity level (PAL), that is, total energy expenditure (TEE) divided by RMR, or the use of analyses of co-variance incorporating measures of body size. The validity of this concept was tested and confirmed in a large database of 574 subjects, where TEE was measured with the precise doubly water method over a 14 d period.[6] Since energy expenditure is mostly expressed per kilogram of body mass, energy expenditure at a certain speed or distance, increases with body mass. However, adjustment of AEE for difference in body size must be exercised with great caution when interpreting AEE data from individuals or groups of markedly different body sizes, since weight$^{1.0}$ overcorrects for size differences.[7]

The gross energy costs of exercise that can be maintained for more than a few minutes, varies roughly between 2.0 METs (leisure walking) and 8.0 METs (running 8 kmph). To expend more energy (for example, 18 METs; running 15 kph) for a longer period of time, the aerobic fitness of an individual has to be far beyond the level that is observed in the general population. An individual with an aerobic fitness of 35 ml/min/kg oxygen uptake, which is the average for a 35-year old female, is not able to expend more than 7 METs continously for more than 30 min. This corresponds with 70% maximal oxygen uptake (VO_2 max). For this individual with this average level of fitness, walking (2–5 METs) is the recommended level of intensity that will be effective in the longterm. However, in obese women, even this level of exercise can be excessive, as was shown by Mattson *et al.*[8] This may also explain the high level of drop outs in training programs with obese subjects who have relatively lower levels of aerobic fitness. This was demonstrated in a study by Westerterp *et al,*[9] on the effect of a 40-week training program to run a half-marathon in lean–moderately obese males and females. Subjects with higher body mass indexes (BMI) were more likely to be early dropouts, especially in the female group. This results in a cycle of decreased physical activity accompanied by a deterioration in aerobic fitness, gradually reducing the ability and desire to perform significant amounts of physical activity.

Based on the aforementioned considerations, one can discuss the potential for physical activity in relation to TEE and fitness. When advising obese subjects to be more active, it seems realistic not to expect any dramatic increases in TEE, for only low- to moderate intensity activities over a relative short period of time are initially achievable. In Table 1, a theoretical calculation is given for a female (aged 35 y) with an average sedentary or active life style, with concomitant average levels of fitness.[10]

For an obese woman of 80 kg with a percentage body fat of 35%, the calculated RMR is about 1440 kcal. Daily EE, originating from physical activity, can be estimated at 500 kcal/d, based on a PAR of 1.5. If the net EE during activity is calculated by subtracting RMR from the total EE, the net energy costs of exercise per hour can roughly be estimated as MET value minus 1 multiplied by the body weight. For this obese woman, 30 min of brisk walking (4–5 METs) will yield an extra 177 kcal, or a PAR increase of 0.12 to about 1.62. If aerobic fitness is improved from 30 to 45 ml/kg VO_2 max through an active lifestyle, the duration time of the activity can be extended from 30–60 min with an intensity

Table 1 Differences in the thermogenic profile of typical sedentary and active female aged 35 y (theoretical calculations)

	Sedentary	*Active*	*% Difference*
Weight (kg)	80	65	− 19
Height (cm)	165	165	—
BMI	29.4	23.8	− 19
Aerobic power (ml/O_2/kg/min)	30	45	+50
RMR (kcal/d)[11]	1440	1330	− 8
Total EE (kcal/d)	2160	2390	+11
PAR	1.5	1.8	+20
AEE (kcal/d)	500	820	+64
Expenditure at 50% VO_2max (kcal/min)	5.9	7.2	+22
METs	4.4	6.6	+50
Activity time (min)	85	114	+34
Extra effect exercise (30 min) at 50% VO_2 max (kcal)	177	216	+22
PAR	1.62	1.96	+21
Resp exchange ratio	0.88	0.83	− 7
Fat oxidation (g)	8	14	+75

Adapted from Saris.[10]
BMI = body mass index; RMR = resting metabolic rate; EE = energy expenditure; PAR = physical activity ratio; AEE = activity EE; METs = multiples of RMR.

corresponding to 50% of maximal aerobic fitness (6.6 METs instead of 5.1 METs). Then an increase from 177 kcal to 528 kcal in extra EE can be expected and the PAR will rise to 1.87. This calculation is based on the assumption that body weight remains high. With higher levels of daily physical activity and a lower body weight, especially body fatness, EE is still considerably higher.

These calculations also clearly illustrate that rapid weight gain, suggesting an extreme energy imbalance, is most probably related to a marked increase in energy intake instead of a decrease in physical activity. For example, a weight gain of 15 kg in one year for a nonobese 65 kg woman, with a PAR of 1.5, would reflect an initial increase in positive energy balance of about 500 kcal/d.[11]

Exercise, substrate utilization and weight control

Experimental evidence suggests, that in addition to the components of energy expenditure in relation to energy intake, substrate utilization also plays an important role in body weight regulation. Both carbohydrates (CHO) and fat, substantially contribute to energy metabolism. Depending on the intensity level of the activity, the contribution to EE changes from nearly 100% fat at rest and low-intensity exercise to almost 100% CHO in high-intensity exercise. From experience with athletes, it is known that the body's capacity to store CHO is very limited in comparison to fat. This has implications for the regulation of the fuel mix that is oxidized, as well as the ability of the overall regulatory system to counteract depletion of CHO stores. Consequently, variation in CHO stores as a result of exercise, has a larger impact on appetite and satiety as has been shown in a mouse model.[12]

From animal and human studies, it has become clear that in contrast to CHO, an increase in fat intake results temporarily in a discrepancy between Food Quotient (FQ) and Respiratory Quotient (RQ). The data suggest that deviation in weight balance can mainly be explained by deviations in fat balance. A well-controlled study in the respiration chamber, looking at the effects of a high fat diet on substrate balance, under strict control of the energy balance, showed a positive fat balance for seven days before RQ matched FQ.[13]

The nutritional habits of Western society are clearly characterized by high dietary fat. Since the health-related recommendation to reduce fat intake to around 30 En% is not likely to be met very soon, special attention should be paid to strategies that would increase the output component of the fat balance: lipid oxidation. Besides certain pharmacological drugs, for example, caffeine, physical activity is by far the best physiological activator of lipid oxidation. In another study, Schrauwen *et al*[14] demonstrated that the depletion of glycogen stores during exercise, stimulated fat oxidation and reduced the period of adaptation to reach steady state FQ = RQ, to at least four days on a high fat diet. It took seven days with low levels of exercise.[13] During low-intensity exercise, a higher proportion of free fatty acid (FFA) is oxidized that is primarily blood born and preferentially oxidized in slow- twitch (type 1) muscle fibers.[15] (See Figure 1).

For example, at 30% VO_2max, the RQ-value is about 0.81, which means that 62% of the total substrate utilization is derived from fat. At higher levels of exercise intensity, more fast-switch (type 2) fibers are involved with a preferential utilization of CHO. At 80% VO_2max, the RQ-value is about 0.91, with only 21% derived from fat. It has, therefore, been argued that low-intensity exercise is optimal for maximizing lipid oxidation. However, more important than the change in the RQ-value, is the increase in EE with increasing intensity. Therefore, the optimal level of fat oxidation, in absolute terms, is likely to be around 60% VO_2max. A study on the impact of exercise intensity on body fatness, showed a larger decrease in subcutaneous skinfolds in a high-intensity training group, compared to an endurance training group, after correction for differences in energy output.[16] More controlled studies with comparable levels of 24 h EE are needed to clarify this important issue. If low intensity exercise was shown to give similar results in terms of 24 h fat oxidation, when compared to moderate–high intensity exercise, this would be valuable for exercise therapy, since low intensity exercise is more acceptable to the obese population.

A further potential mechanism for increasing capacity to oxidize fat, is physical training and improved endurance fitness, as it results in a shift from CHO to fat oxidation at the same relative workload intensity. Martin *et al*[17] demonstrated a shift in lipid oxidation from 38–58% at the same relative intensity of exercise, after a training period of only 12 weeks[19] (see Figure 2). The underlying mechanisms for these training-induced adaptations probably involve changes in muscle respiratory capacity and hormonal adaptations. Increases in the muscle content

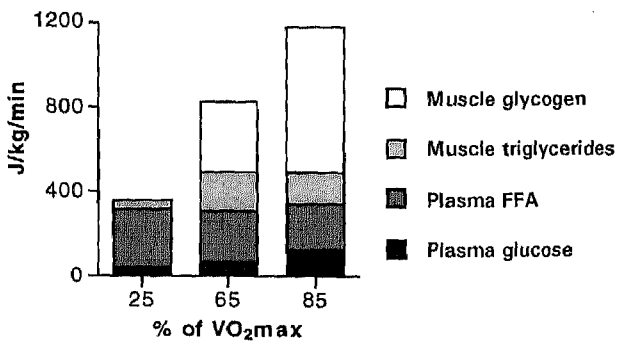

Figure 1 Substrate source and utilization at different exercise intensities after 30 min of cycling exercise. J/kg/min =; VO_2max =; FFA = free fatty acids. Adapted from Romijn *et al*.[15]

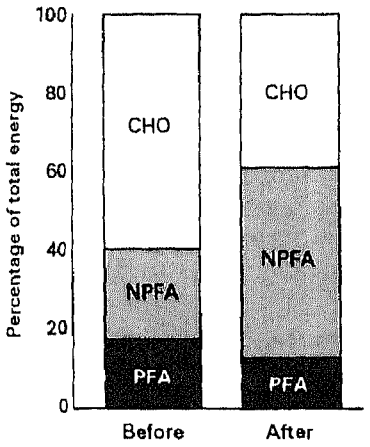

Figure 2 Percentage of total energy derived from carbohydrate (CHO) and non-plasma and plasma fatty acid (NPFA and PFA) fuel source during prolonged exercise at 63% VO_2 max before and after 12 weeks of endurance training. Adapted from Martin *et al.*[17]

of mitochondria enzymes involved in activation transfer into mitochondria and beta-oxidation of fatty acids, increases in cytosolic fatty acid binding protein, and change in activity of regulatory molecules, such as malonylCoA, also occur with training.[18] Furthermore, training increases the capacity to store triglycerides in muscles of humans.[19]

Based on these results, one can estimate the extra fat oxidation during 30 min of exercise at 50% VO_2 max, using the examples provided in Table 1. This gives a difference of 6 g fat per day (+75%) for this extra bout of exercise. However, this does not necessarily mean that these extra fat stores are originated from the adipose tissue. Based on Figure 2, one can conclude that the extra fat oxidation is primarily non-plasma fatty acid oxidation, which means intra-muscular triglycerides (IMTG). Martin *et al*[17] concluded that the lower plasma FFA oxidation is related to the lower rate of FFA release from adipose tissue. Reduction in blood flow may entrap FFA in the fat cell, since directly after cessation of the exercise, a sharp rise in plasma FFA concentration is normally seen. This also implies that muscle triglyceride stores are important in relation to substrate utilization as an individual becomes more active. The factors which regulate IMTG oxidation and determine the relative contribution of FFA *vs* IMTG to fat oxidation is not well understood. However, IMTG appears to be utilized more during the initial phase of moderate exercise, with an increasing contribution from circulating FFA as time progresses.[20]

In the long term, excess intake of fat or impairment in fat oxidation, leads to a substantial change in the composition of the fuel mix oxidized, which itself contributes to the achievement of a new plateau of weight with a higher percentage of body fat. Schutz *et al*[21] concluded that a weight gain or loss of 10 kg of fat mass was accompanied by a mean change in lipid oxidation of about 20 g/d. Compared to an untrained individual, a trained individual oxidizes this extra amount of fat during 60 min of moderate exercise, as can be calculated from the study of Martin *et al.*[17] This demonstrates the potential role of exercise in the maintenance of a lower fat mass without compromising habitual fat intake.

Fatness, the capacity to oxidize fat and exercise

The individual variation in the metabolic capacity to use fat as an energy substrate, may play a crucial role in the regulation of energy balance. Several studies have indicated now that, in comparison to lean individuals, fat oxidation is impaired in the obese or post-obese. In the study of Lean and James,[22] the post-obese subjects had at energy balance, a lipid oxidation rate of 2.6 g/kg FFM per day, compared to the 3.1 g/kg FFM and 3.0 g/kg FFM in the lean and obese group respectively. It is important to emphasize that, the relative lipid oxidation was comparable to lean and obese subjects. This illustrates again the generally accepted idea that obesity *per se* may potentially correct a deficit in lipid oxidation, with the consequence that a higher lipid balance can be achieved under high fat diets. Blaak *et al*[23] have shown that in obese or post-obese individuals, lipid oxidation in muscle is impaired after a β-adrenergic stimulation. This observation was confirmed by Colberg *et al*,[24] who found a reduced post-absorptive lipid utilization in leg muscle of women with visceral obesity. Also, Zurlo *et al*[25] found that 24 h RQ-values correlated negatively with skeletal muscle activity of β-hydroxyacylcoenzyme A dehydrogenase, a key enzyme in the β-oxidation. There is surprisingly little information about the substrate utilization of obese compared to lean individuals during exercise. A study of Wade *et al*[26] showed that fatter men, who had a relative low percentage of type I muscle fibres, oxidized less fat at an absolute workload of 100 Watt, compared to leaner men with a higher percentage of type I muscle fibres. However, other studies have failed to reproduce these findings. Geerlings *et al*[27] found no correlation between percentage body fat and respiratory exchange ratio during exercise in sedentary men with a much larger variation in body fat than in Wade's study. Simoneau and Bouchard[28] did not demonstrate a difference in percentage type I muscle fibres in men with a low and high subcutaneous fat matched for VO_2 max. These results suggest that fat utilization during exercise is similar in obese and lean individuals at the same relative exercise intensity and physical fitness. However, from this finding it is difficult to conclude whether this apparently normal substrate utilization during exercise in the obese, is dependent on a high body fat mass. To answer this question, substrate utilization needs to be studied in the pre-obese or in the post-obese state. These data are not available at this moment.

More controlled respiration chamber studies are needed to quantitate the extra lipid oxidation depending on the level of exercise duration, intensity and fitness. We also need more detailed quantitative data on the post-exercise period. It makes sense that post-exercise metabolism is devoted to replenishing CHO stores, leading to a decrease in CHO oxidation and a compensatory increase in lipid oxidation. Based on these observations and theoretical considerations, it can be postulated that short bouts of high intensity exercise with long slow intervals, should activate fat oxidation more than an equi-energetic long-term continuous low intensity exercise session.

Also the effect of gender on exercising fuel metabolism needs further attention in research. A few studies have found that females, in comparison to males, oxidize proportionally more lipids during an exercise session of a similar intensity. Maybe this has to do with the gender-related differences in body composition, although this has not always been observed.[29] Of importance in this respect, is the consistent observation of a gender difference in the effect of training on body weight. In a study on the effects of a long-term endurance training programme, a much higher metabolic response was found in males than in females.[30] In males, the reduction in body fat was 4.2 kg over the 10-month training period. For females, however, reduction in body fat was 2.4 kg for the same time period. It was suggested that in males, exercise leads to a stimulation of EE associated with extra physical activity outside the training hours, whereas in females, such an effect could not be found. Gender differences in body composition changes and adipose tissue function were also noticed in a 20-week aerobic exercise programme.[31] Males demonstrated a significant reduction in body weight, fat mass and fat cell weight. Epinephrine-stimulated lipolysis was considerably more enhanced in males (+66%) than in females (+46%).[32]

Differences in distribution of adipose tissue may be a key factor to the variance in response. In relation to exercise, abdominal fat cells are more sensitive to β-adrenoceptor activity. In females, storage capacity is primarily located in the femoral regain, particularly where β-adrenoceptors are less dominant. There seems to be consensus in the literature that, females are more resistant to fat loss during exercise compared to males. However, controlled studies that allow us to unravel the metabolic and behavioural factors involved in this gender difference are lacking.

Level of physical activity and body weight regulation

There is little questioning that modern inactive life styles are heavily implicated in the etiology of obesity. As a corollary of this, it would be expected that exercise and high levels of physical activity should protect against inappropriate weight gain. Several prospective studies, some with cross-sectional elements, have addressed this question.[33–35] Some of the findings are inconclusive, most probably related to the result of inadequacies in the techniques for assessing physical activity in epidemiological settings. The three studies with the largest samples and longest follow-up periods show clear inverse associations with physical activity and weight gain, with odd;

Table 2 Prospective studies showing protective effect of physical activity against weight gain

		Weight change (kg)		*Odds ratio for excess gain*	
Study	*Activity*	*Men*	*Women*	*Men*	*Women*
Rissanen *et al*[33]	frequent	− 0.1	− 0.6	1.0	1.0
6165 men, 6504 women	occasional	0.6	0.0	1.5	1.5
	rare	1.0	0.3	1.9	1.6
5.7 y follow-up					
Excess gain = > 5 kg					
Williamson *et al*[34]	*At follow-up*				
3515 men, 5810 women.	high	0.0	0.0	1.0	1.0
	moderate	0.9	1.4	1.8	2.5
10 y follow-up.	low	1.6	1.9	3.1	3.8
Excess gain = > 13 kg					
	Change from baseline				
	stayed high	0.0	0.0	1.0	1.0
	decreased	1.4	1.9	2.3	6.2
Haapanen *et al*[35]	*Leisure time activity at follow-up*				
2564 men, 2695 women	high	1.3	1.1	1.0	1.0
	moderate	1.8	1.3	1.7	2.0
10 y follow-up	low	2.5	1.7	2.6	2.7
Excess gain = > 5 kg					
	Change from baseline				
	stayed high	0.0	0.0	1.0	1.0
	decreased	1.5	1.8	2.0	2.5
	became active	− 0.1	0.5	1.1	1.1
	inactive all time	1.2	0.3	1.6	1.6

ratios for excess weight gain ranging from 1.6–6.2 (see Table 2).

However, it should be noted that even in these studies, levels of significance were marginal, reflecting imprecision in the measurements of activity and the multiplicity of factors influencing weight change. Only the study of Haapanen *et al*[35] showed clear and significant differences based on the measurement of leisure time activities.

Recently, three studies were published on the relationship between PAR and body fatness, based on the doubly labeled water technique, which is now considered as the gold standard for the measurement of daily physical activity.[36–38] Each study showed a significant negative relationship between physical activity and body fatness. In the study of Westerterp and Goran,[38] this relationship was found to be significant in males only. In the study of Schulz and Schoeller,[36] stepwise multiple regression demonstrated that FFM and age explain 65% of the variation in daily EE. Even more important was the strong negative relationship between body fatness and non-basal energy expenditure divided by weight. Although the data was a compilation of very extreme groups such as Pima Indians (who are known to be prone to become obese), athletes during an extreme cycling race or healthy individuals in developing countries, the absence of overweight individuals above the expenditure level of around 0.1 MJ/kg/d was remarkable. Based on this arbitrary threshold of 0.1 MJ/kg/d, one can calculate the level of activity needed to meet this criteria.

Taking the theoretical example of an active woman in Table 1, non-resting energy expenditure based on this threshold is around 1500 kcal. Assuming that the TEF is about 10% of TEE (285 kcal), the net energy expenditure for physical activity is 1215 kcal. This active woman probably has an average aerobic fitness of about 45 ml.O_2/kg/min. To spend 1215 kcal at a moderate level of exercise (50% VO_2 max), will take her about 170 min or almost 3 h. Even assuming that during a normal day, approximately 2 h of physical activity (standing, walking, etc. at 25% VO_2 max) are spent at a low level and at an energy cost of 435 kcal, the remaining AEE (780 kcal) will take another 105 min at a moderate intensity level.

Schoeller *et al*[39] have addressed this question, while looking at the level of AEE to minimize weight gain in previously obese women. Retrospective analyses of weight gain as a function of AEE, indicated a threshold for weight maintenance of 11 kcal/kg body weight/d, which corresponds to 740 kcal/d. This result is comparable to the theoretical assumptions in Table 1. It strengthens the conclusion that a substantial increase in the daily levels of physical activity is obligatory for the general public, in order to keep metabolic control on body weight when functioning in unfavorable environmental conditions, such as the availability of an abundant relative high fat diet.

Long-term effect of physical activity on weight maintenance

The most striking and consistent finding in support of a beneficial role for physical activity in the management of obesity, is the relationship of physical activity to long-term weight control. A significantly larger percentage of those women who were successful at weight loss and weight maintenance, exercised regularly, compared to those women from the same weight loss programme who regained weight.[40] Self-reported data from successful reduced-obese subjects in the National Weight Control Registry, report expending an average of 2800 kcal/week in physical activity.[41] However, many studies have used non-randomized observations and might simply be reflecting the fact that people who incorporate exercise into their personal weight control strategy, are the most highly motivated persons. Findings from controlled intervention studies, demonstrated that those participants who continued to exercise, maintained their weight loss over time, relative to those who did not continue.[42–45] In fact, physical activity may be a more successful follow-up strategy than dietary approaches.[46] However, information is lacking on mechanisms, even though it is known that exercise induces a number of favorable physiological alterations. Relatively less is known about the psychological factors, which most likely have a substantial effect on weight control as well.[47] Suggested mechanisms include the possible influence of activity on dietary control, as well as the psychological mechanisms, such as mood, self esteem and self-efficacy.[48,49]

The current recommendation for physical activity in adults in the US is $\geq$30 min moderate intense physical activity, preferable on all days of the week.[50] This recommendation fulfills the minimum criteria necessary to sustain an active life style. Based on the available studies so far, such a recommendation, while of minimal importance in acute weight loss, could play a major role in determining the success of long-term weight maintenance.

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